UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/511,914 | 09/06/2005 | Scott A Loiler | 36689.37 | 2333 |

27683 7590 08/03/2009

HAYNES AND BOONE, LLP
IP Section
2323 Victory Avenue
Suite 700
Dallas, TX 75219

| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/03/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/511,914 | LOILER ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-4,6-8,16,19,20,22-24,28,44 and 52-60* is/are pending in the application.

4a) Of the above claim(s) *52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,7,8,16,19,20,22-24,28,44 and 54-59* is/are rejected.

7)☒ Claim(s) *6 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-18-04,1-31-05,10-11-05,& 9-11-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of group II, claim 44, in the reply filed on 5-18-09 is acknowledged. The traversal is on the ground(s) that applicants cite PCT Rule 13.1 and 37 C.F.R. 1,475 and argue that there is no lack of unity of the invention as the pending claims are drawn to a product and to methods for their use. The unity of invention has to be construed in relation to the independent claims in an international application and not the dependent claims. This is not found persuasive because the putative special technical feature common to group I-IV is a recombinant AAV viral vector comprising a nucleic acid encoding an amino acid sequence that binds to a mammalian lipoprotein receptor, which is an independent claim (original claim 1). Zuckerman et al., 2008 (US Patent No. 7,462,592) discloses using s vector, targeting ligands and polycationic agents to increase the delivery of a polynucleotide to a target cell (e.g. abstract). The vector can be AAV vector (e.g. description paragraph 45). Lipoprotein can be used to target the delivery of the polynucleotide to cells expressing lipoprotein receptor (e.g. description paragraph 162). Therefore, there is no special technical feature that is contributed by the instant invention over the prior art. Applicants argue that the "further restriction" is improper, each of the disclosed sequences represents the primary amino acid sequence of an ApoE or ApoE-homologous peptide, or a consensus sequence thereof and those sequences can be aligned to produce a consensus peptide sequence such that they are species of a genus. Upon further consideration of the sequences, the "further restriction" requirement has been withdrawn; however, election of species is required. As indicated by applicants that "if the 'further restriction' requirement were vacated, and an election of species requirement made of record,

Applicants would accept, with traverse, the election provided herein" (Response/Remarks, p. 17). Applicants elect SEQ ID No. 10 for election of species (Response/Remarks, p. 18). Therefore, group II and species SEQ ID No. 10 have been elected for examination in the instant invention.

Since claims 52 and 53 are drawn to nucleotide sequence of SEQ ID No. 1, which is non-elected species, therefore, claims 52 and 53 are withdrawn from consideration at this time.

Applicants' amendment filed 5-18-09 has been entered. Claims 1, 10-15, 30, 32, 33, 43, 45 and 47 have been canceled. Claims 2-4, 6-8, 16, 19, 20, 22-24, 28 and 44 have been amended. Claims 52-60 have been added. Claims 2-4, 6-8, 16, 19, 20, 22-24, 28, 44 and 52-60 are pending. Since claims 2-4, 6-8, 16, 19, 20, 22-24 and 28 have been amended to depend from claim 44, claims 2-4, 6-8, 16, 19, 20, 22-24, 28, 44 and 54-60 and SEQ ID No. 10 are under consideration.

### *Information Disclosure Statement*

2. The information disclosure statement (IDS) submitted on 10-18-04, 1-31-05, 10-11-05 and 9-11-07 were filed before the first Official action. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8, 16, 19, 20, 22-24, 28, 54 and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 8, 16, 19, 20, 22-24, 28, 54 and 55 are directed to a method for targeting an AAV virion or viral particle to a mammalian cell comprising cell-surface lipoprotein receptor comprising providing a population of cells an AAV vector comprising a nucleic acid encoding an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor in an amount effective to target said virion or said viral particle to the cell expressing said cell-surface lipoprotein receptor. Claim 8 specifies the vector further comprises a second polynucleotide comprising a second nucleic acid segment encoding an expressed therapeutic agent. Claim 16 specifies the second polynucleotide further comprises a promoter operably linked to said second nucleic acid segment. Claim 19 specifies the promoter comprises a mammalian or chicken beta-actin promoter. Claims 20 and 22 specify the second polynucleotide further comprises an enhancer operably linked to the second nucleic acid segment and the enhancer comprises a CMV enhancer, respectively. Claims 23 and 24 specify the second nucleic acid segment further comprises a post-transcriptional regulatory sequence and a woodchuck hepatitis virus post-transcriptional regulatory element, respectively. Claims 28 and 54 specify the therapeutic agent is an alpha1-antitrypsin (AAT) polypeptide and a human alpha1-antitrypsin polypeptide, respectively. Claim 55 specifies the promoter comprises a chicken beta-actin promoter.

The claims read on administering an AAV virion or viral particle comprising a nucleotide sequence encoding a therapeutic agent under the control of a promoter or an enhancer to mammalian cells in vivo. The specification states "[t]he present invention relates generally to the fields of molecular biology and virology and in particular, to methods for using recombinant adeno-associated virus (rAAV) compositions that express nucleic acid segments encoding

therapeutic gene products in the treatment of complex human disorders. In certain embodiments, the invention concerns the use of rAAV in a variety of investigative, diagnostic and therapeutic regimens, including the treatment of diseases of the pancreas and diabetes. Methods and compositions are also provided … for use in a variety of viral-based gene therapies, and in particular, treatment and/pr preventions of human diseases and disorders such as diabetes" (e.g. specification, p. 1). The administration of the AAV virion expressing a therapeutic agent to mammalian cells in vivo apparently is intended for gene therapy of various human diseases or disorders, such as diabetes. The claims read on gene therapy in vivo and the specification fails to provide adequate guidance and evidence for how to treat or prevent various human diseases or disorders by administering an AAV virion expressing a therapeutic agent to mammalian cells in vivo. The specification also fails to provide a correlation between the therapeutic agent and the diseases or disorders treated in vivo.

The claims read on gene therapy by using AAV for treating various diseases and disorders in vivo. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a

resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

The claims encompass treating diseases or disorders at various locations in a subject. Administration route plays a very important role in determining whether sufficient protein of interest can be expressed and present at the target cells at various locations in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) reports that numerous factors complicate in vivo gene transfer with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy" (e.g. abstract).

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to treat various diseases or disorders by administering AAV expressing

various therapeutic agents under the control of various promoters or enhancers via various administration routes in vivo.

Further, it was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the

structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. Different proteins have different biological functions and whether a therapeutic protein encoding gene can be used for treating a particular disease and disorder depends on the particular biological function of the therapeutic protein and the disease and disorder treated. Absent specific guidance for the correlation between the therapeutic protein encoding gene and the diseases and disorders, one skilled in the art at the time of the invention would not know how to use the claimed method to treat numerous different diseases and disorders in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

### *Claim Rejections - 35 USC § 102*

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 2, 3, 8, 44 and 56-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al., 2000 (Blood, Vol. 96, No. 1, part1, pp. 431a).

Claims 2, 3, 8, 44 and 56-59 are directed to a method for targeting an AAV virion or viral particle to a mammalian cell comprising cell-surface lipoprotein receptor comprising providing a population of cells or mammalian cells or human host cells an AAV vector comprising a nucleic acid encoding an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor in an amount effective to target said virion or said viral particle to the cell expressing said cell-surface lipoprotein receptor. Claim 2 specifies the AAV capsid protein comprises a Vp1 or a VP2 capsid protein. Claim 3 specifies the exogenous amino acid sequence binds to a mammalian LDL or VLDL receptor. Claim 8 specifies the vector further comprises a second polynucleotide comprising a second nucleic acid segment encoding an expressed therapeutic agent. Claim 56 specifies the vector is within an AAV virion or viral particle. Claim 59 specifies the exogenous amino acid sequence comprises at least a first contiguous amino acid sequence from SEQ ID No. 9 or 10.

Anderson teaches that adeno-associated virus type 2 (AAV-2) is a vector with great promise for many gene therapy protocols due to wide tropism but AAV-2 shows poor tropisim to haematopoietic cells. Anderson discloses identification of the optimized peptide sequence RHLRKLRKRLAR from one of the ligands for LDL-R, apolipoprotein E. Anderson teaches inserting oligonucleotide encoding the RHLRKLRKRLAR peptide into different regions of the VP1 gene to produce seven different targeted recombinant AAV-2 viruses containing the cDNA for GFP. Anderson shows that the targeted viruses are able to deliver GFP DNA in virion dependent manner to U937 cells, enhancing the susceptibility of these cells by at least 4 orders of

magnitude. U937 is a human leukemic monocyte lymphoma cell line. GFP can be considered a therapeutic agent. The phrase "at least a first contiguous amino acid sequence from SEQ ID No. 9 or 10" in claim 59 is interpreted as **any two or more contiguous amino acid residues** from SEQ ID No. 10 (SEQ ID No. 10 is elected species) because any two or more contiguous amino acid residues is considered a contiguous amino acid sequence. The amino acid sequence RHLRKLRKRLAR has at least two contiguous amino acid residues that are 100% identical to two or more amino acid residues from SEQ ID No. 10. Anderson teaches every element of the claimed invention. Thus, the claims are anticipated by Anderson.

### *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 8, 16, 20, 28, 44 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2000 (Blood, Vol. 96, No. 1, part1, pp. 431a) in view of Srivastava et al., 1998 (WO 98/09524).

Claims 8, 16, 20, 28, 44 and 54 are directed to a method for targeting an AAV virion or viral particle to a mammalian cell comprising cell-surface lipoprotein receptor comprising providing a population of cells an AAV vector comprising a nucleic acid encoding an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor in an amount effective to target said virion or said viral particle to the cell expressing said cell-surface lipoprotein receptor. Claim 8 specifies the vector further comprises a second polynucleotide comprising a second nucleic acid segment encoding an expressed therapeutic agent. Claim 16 specifies the second polynucleotide further comprises a promoter operably linked to said second nucleic acid segment. Claim 20 specifies the second polynucleotide further comprises an enhancer operably linked to the second nucleic acid segment. Claims 28 and 54 specify the therapeutic agent is an alpha1-antitrypsin (AAT) polypeptide and a human alpha1-antitrypsin polypeptide, respectively.

Anderson teaches that adeno-associated virus type 2 (AAV-2) is a vector with great promise for many gene therapy protocols due to wide tropism but AAV-2 shows poor tropisim to haematopoietic cells. Anderson discloses identification of the optimized peptide sequence RHLRKLRKRLAR from one of the ligands for LDL-R, apolipoprotein E. Anderson teaches inserting oligonucleotide encoding the RHLRKLRKRLAR peptide into different regions of the VP1 gene to produce seven different targeted recombinant AAV-2 viruses containing the cDNA for GFP. Anderson shows that the targeted viruses are able to deliver GFP DNA in virion

dependent manner to U937 cells, enhancing the susceptibility of these cells by at least 4 orders of magnitude. U937 is a human leukemic monocyte lymphoma cell line. GFP can be considered a therapeutic agent.

Anderson does not specifically teach using a promoter or enhancer operably linked to the second nucleic acid segment encoding a therapeutic agent or the therapeutic agent is an alpha1-antitrypsin or a human alpha1-antitrypsin polypeptide.

Srivastava teaches a method of administering an AAV vector expressing a therapeutic molecule, such as alpha1-antitrypsin, to a mammalian patient having a need for liver expression of a therapeutic molecule (e.g. abstract, p. 4, 2nd paragraph). Srivastava teaches using an AAV vector containing a liver specific promoter operably linked to the nucleic acid encoding the therapeutic molecule, for example, alpha fetal protein gene promoter, albumin gene promoter and alpha-1 antitrypsin gene promoter, and their respective enhancer (e.g. p. 7-8).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare an AAV vector or virion containing a second nucleic acid encoding a therapeutic agent, such as alpha1-antitrypsin, under the control of a mammalian promoter or an enhancer because Anderson teaches that adeno-associated virus type 2 (AAV-2) is a vector with great promise for many gene therapy and Srivastava teaches administering an AAV vector expressing a therapeutic molecule, such as alpha1-antitrypsin, under the control of a promoter, such as albumin gene promoter, or enhancer to a mammalian patient for liver specific expression. It also would have been prima facie obvious for one of ordinary skill in the art to use a nucleic acid encoding a human alpha1-antitrpsin because Srivastava teaches using a nucleic acid

encoding alpha1-antitrpsin and it would be obvious to use alpha1-antitrpsin gene from different organisms including humans.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to use AAV vector as a delivering vehicle for liver specific expression of a therapeutic molecule as taught by Srivastava or use AAV vector or virion for gene expression in U937 cells as taught by Anderson with reasonable expectation of success.

10. Claims 8, 16, 19, 20, 22-24, 44 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2000 (Blood, Vol. 96, No. 1, part1, pp. 431a) in view of Zolotukhin et al., 2005 (US Patent No. 6,967,018 B2).

Claims 8, 16, 19, 20, 22-24, 44 and 55 are directed to a method for targeting an AAV virion or viral particle to a mammalian cell comprising cell-surface lipoprotein receptor comprising providing a population of cells an AAV vector comprising a nucleic acid encoding an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor in an amount effective to target said virion or said viral particle to the cell expressing said cell-surface lipoprotein receptor. Claim 8 specifies the vector further comprises a second polynucleotide comprising a second nucleic acid segment encoding an expressed therapeutic agent. Claim 16 specifies the second polynucleotide further comprises a promoter operably linked to said second nucleic acid segment. Claim 19 specifies the promoter comprises a mammalian or chicken beta-actin promoter. Claims 20 and 22 specify the second polynucleotide further comprises an enhancer operably linked to the second nucleic acid segment and the enhancer comprises a CMV enhancer, respectively. Claims 23 and 24 specify the second

nucleic acid segment further comprises a post-transcriptional regulatory sequence and a woodchuck hepatitis virus post-transcriptional regulatory element, respectively. Claim 55 specifies the promoter comprises a chicken beta-actin promoter.

Anderson teaches that adeno-associated virus type 2 (AAV-2) is a vector with great promise for many gene therapy protocols due to wide tropism but AAV-2 shows poor tropisim to haematopoietic cells. Anderson discloses identification of the optimized peptide sequence RHLRKLRKRLAR from one of the ligands for LDL-R, apolipoprotein E. Anderson teaches inserting oligonucleotide encoding the RHLRKLRKRLAR peptide into different regions of the VP1 gene to produce seven different targeted recombinant AAV-2 viruses containing the cDNA for GFP. Anderson shows that the targeted viruses are able to deliver GFP DNA in virion dependent manner to U937 cells, enhancing the susceptibility of these cells by at least 4 orders of magnitude. U937 is a human leukemic monocyte lymphoma cell line.

Anderson does not specifically teach using a mammalian or chicken beta-actin promoter, a CMV enhancer or a woodchuck hepatitis virus post-transcriptional regulatory element in an AAV vector.

Zolotukhin teaches that a chicken beta-actin promoter or a CMV enhancer operably linked to a nucleotide sequence can be used for liver-specific or muscle specific expression (Brief Summary Text (11)). Zolotukhin also teaches preparation of an AAV transfer vector containing mouse adiponectin cDNA (Acrp30) under the control of a chicken beta-actin promoter linked to a CMV enhancer for liver specific expression and a woodchuck hepatitis virus post-transcriptional regulatory sequence (WPRE) to enhance expression of the transgene (e.g. Figure 1, Detailed Description Text (52) and (53)).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare an AAV vector or virion containing a mammalian or chicken beta-actin promoter, a CMV enhancer or a woodchuck hepatitis virus post-transcriptional regulatory element because Zolotukhin teaches preparation of an AAV transfer vector containing mouse adiponectin cDNA (Acrp30) under the control of a chicken beta-actin promoter linked to a CMV enhancer for liver specific expression and a woodchuck hepatitis virus post-transcriptional regulatory sequence (WPRE) to enhance expression of the transgene and Acrp30 can be considered a therapeutic agent.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to obtain liver specific expression of a transgene and to enhance expression of said transgene as taught by Zolotukhin with reasonable expectation of success.

11. Claims 4, 7 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2000 (Blood, Vol. 96, No. 1, part1, pp. 431a) in view of Laskowitz et al., 1999, Geneseq Accession No. AAY33245 (computer printout p. 26-27).

Claims 4, 7 and 44 are directed to a method for targeting an AAV virion or viral particle to a mammalian cell comprising cell-surface lipoprotein receptor comprising providing a population of cells an AAV vector comprising a nucleic acid encoding an AAV capsid protein that comprises an exogenous amino acid sequence that binds to a mammalian lipoprotein receptor in an amount effective to target said virion or said viral particle to the cell expressing said cell-surface lipoprotein receptor. Claim 4 specifies said exogenous amino acid sequence comprises the sequence of any one of SEQ ID No. 1 to SEQ ID No. 10. Claim 7 specifies the

exogenous amino acid sequence comprises the sequence of SEQ ID No. 9 or 10. It is noted that SEQ ID No. 10 is elected species.

Anderson teaches that adeno-associated virus type 2 (AAV-2) is a vector with great promise for many gene therapy protocols due to wide tropism but AAV-2 shows poor tropisim to haematopoietic cells. Anderson discloses identification of the optimized peptide sequence RHLRKLRKRLAR from one of the ligands for LDL-R, apolipoprotein E. Anderson teaches inserting oligonucleotide encoding the RHLRKLRKRLAR peptide into different regions of the VP1 gene to produce seven different targeted recombinant AAV-2 viruses containing the cDNA for GFP. Anderson shows that the targeted viruses are able to deliver GFP DNA in virion dependent manner to U937 cells, enhancing the susceptibility of these cells by at least 4 orders of magnitude. U937 is a human leukemic monocyte lymphoma cell line.

Anderson does not specifically teach the sequence of SEQ ID No. 10.

Laskowitz discloses the amino acid sequence of human ApoE peptide fragment, Geneseq Accession No. AAY33245, which is 100% identical to the sequence of SEQ ID No. 10 from amino acid residues 7-19. The human ApoE peptide fragment binds to LDL receptor.

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use the oligonucleotide sequence encoding the sequence of SEQ ID No. 10 in an AAV vector because Anderson teaches using oligonucleotides encoding the RHLRKLRKRLAR peptide from ApoE into different regions of the VP1 gene to produce different targeted recombinant AAV-2 viruses and both RHLRKLRKRLAR and SEQ ID No. 10 are from ApoE and both bind to LDL receptor. It would be obvious for one of ordinary skill to substitute one with another.

One having ordinary skill in the art a the time the invention was made would have been motivated to do so in order to use AAV viruses to deliver GFP DNA to U937 cells as taught by Anderson with reasonable expectation of success.

***Conclusion***

12. Claims 2-4, 7, 8, 16, 19, 20, 22-24, 28, 44 and 54-59 are rejected. Claims 6 and 60 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.
/Shin-Lin Chen/
Primary Examiner
Art Unit 1632